FORM PTO-1390 (REV 5-93)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY DOCKET NO. P1614-7038
	TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	DATE: August 4, 1997
		U.S. APPLN. NO. (IF KNOWN, SEE 37 CFR 1.5) 08/875603

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP96/00498	February 7, 1996	February 8, 1995

TITLE OF INVENTION: USE OF CARBAZOLE COMPOUNDS FOR THE TREATMENT OF CONGESTIVE HEART FAILURE

APPLICANT(S) FOR DO/EO/US: Mary Ann LUKAS-LASKEY, Robert RUFFOLO, Jr., Neil SHUSTERMAN, Gisbert SPONER and Klaus STREIN

1. X This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
   (THE BASIC FILING FEE IS ATTACHED)

2. _ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. X This express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT articles 22 and 39(1).

4. X A proper demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. X A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. X is transmitted herewith (required only if not transmitted by the International Bureau).
   b. _ has been transmitted by the International Bureau.
   c. _ is not required, as the application was filed in the United States Receiving Office (RO/US)

6. _ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. _ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. _ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. _ have been transmitted by the International Bureau.
   c. _ have not been made; however, the time limit for making such amendments has NOT expired.
   d. _ have not been made and will not be made.

8. _ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. _ An oath or declaration of the inventor(s) (35 U.S>C. 371(c)(4)).

10. _ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. X An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. _ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. X A FIRST preliminary amendment.
    _ A SECOND or SUBSEQUENT preliminary amendment.

14. _ A substitute specification.

15. _ A change of power of attorney and/or address letter.

16. X Other items or information: PCT/IPEA/401, PCT/IPEA/416, PCT/IPEA/409, PCT/RO/105, PCT/RO/101, PCT/ISA/210, PCT/ISA/220 Check No. 14073

U.S. APPLN. NO. (IF KNOWN, SEE 37 C.F.R. 1.50)	INTERNATIONAL APPLICATION NO. PCT/EP96/00498	ATTORNEY DOCKET NO. P1614-7038 DATE: August 4, 1997

17. xx The following fees are submitted: **Basic National Fee (37 CFR 1.492(a)(1)-(5):** Search Report has been prepared by the EPO or JPO.....$910.00 International preliminary examination fee paid to USPTO (37 CFR 1.482)....$700.00 No international preliminary examination fee paid to USPTO (37 CFR1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))....$770.00 Neither international preliminary examination fee (37 CFR 1.482) or international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....$1,040.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) .....$ 96.00	CALCULATIONS | PTO USE ONLY

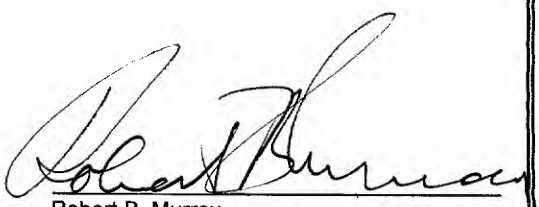
ENTER APPROPRIATE BASIC FEE AMOUNT = 6				$910.00	
Surcharge of $130.00 for furnishing the oath or declaration later than _ 20 _ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$0	
Claims	Number Filed	Number Extra	Rate		
Total Claims	27 - 20 =	7	X $ 22.00	$154.00	
Independent Claims	6 - 3 =	3	X $ 80.00	$240.00	
Multiple dependent claim(s) (if applicable)			+ $260.00	$0	
TOTAL OF ABOVE CALCULATIONS =				$1,304.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$0	
SUBTOTAL =				$1,304.00	
Processing fee of $130.00 for furnishing the English translation later the _ 20 _ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$0	
TOTAL NATIONAL FEE =				$1,304.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +				$0	
TOTAL FEES ENCLOSED =				$1,304.00	
				Amount to be refunded	$
				Charged	$

a. X A check in the amount of $1,304.00 to cover the above fees is enclosed.
b. _ Please charge my Deposit Account No. 14-1060 in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.
c. X The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-1060 .

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

NIKAIDO, MARMELSTEIN, MURRAY AND ORAM
Metropolitan Square
655 15th Street, N.W.
Suite 330 - G Street Lobby
Washington, D.C. 20005-5701
Telephone No. (202) 638-5000



Robert B. Murray
Reg. No. 22,980

103 Rec'd PCT/PTO 29 DEC 1997

SV

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#3

FORM PTO-1390 (REV 5-93)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY DOCKET NO. P1614-7038
	TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	DATE: December 29, 1997
		U.S. APPLN. NO. (IF KNOWN, SEE 37 CFR 1.5) 08/875,603

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP96/00498	February 7, 1996	February 8, 1995

TITLE OF INVENTION: USE OF CARBAZOLE COMPOUNDS FOR THE TREATMENT OF CONGESTIVE HEART FAILURE

APPLICANT(S) FOR DO/EO/US: Mary Ann LUKAS-LASKEY, Robert RUFFOLO, Jr., Neil SHUSTERMAN, Gisbert SPONER and Klaus STREIN

1. _ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
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   a. _ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. _ have been transmitted by the International Bureau.
   c. _ have not been made; however, the time limit for making such amendments has NOT expired.
   d. _ have not been made and will not be made.

8. _ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

01/21/1998 KBLNGEN1 00000058 08875603 inventor(s) (35 U.S>C. 371(c)(4)).
01 FC:154 130.00 OP

10. _ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. X An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. X An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. _ A FIRST preliminary amendment.
_ A SECOND or SUBSEQUENT preliminary amendment.

14. _ A substitute specification.

15. _ A change of power of attorney and/or address letter.

16. _ Other items or information: Notification of Missing Requirements, one month Extension of Time
Check No. 15389

U.S. APPLN. NO. (IF KNOWN, SEE 37 C.F.R. 1.50) 08/875,603	INTERNATIONAL APPLICATION NO. PCT/EP96/00498	ATTORNEY DOCKET NO. P1614-7038 DATE: December 29, 1997

17. xx The following fees are submitted: **Basic National Fee (37 CFR 1.492(a)(1)-(5):** Search Report has been prepared by the EPO or JPO.....$910.00 International preliminary examination fee paid to USPTO (37 CFR 1.482)....$700.00 No international preliminary examination fee paid to USPTO (37 CFR1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))....$770.00 Neither international preliminary examination fee (37 CFR 1.482) or international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....$1,040.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) .....$ 96.00	CALCULATIONS | PTO USE ONLY	
ENTER APPROPRIATE BASIC FEE AMOUNT = 6	$00	
Surcharge of $130.00 for furnishing the oath or declaration later than _ 20 _ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$130	

Claims	Number Filed	Number Extra	Rate		
Total Claims	27 - 20 =	7	X $ 22.00	$00	
Independent Claims	6 - 3 =	3	X $ 80.00	$00	
Multiple dependent claim(s) (if applicable)			+ $260.00	$00	
TOTAL OF ABOVE CALCULATIONS =				$00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$00	
SUBTOTAL =				$130.00	
Processing fee of $130.00 for furnishing the English translation later the _ 20 _ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$0	
TOTAL NATIONAL FEE =				$130.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +				$40	
TOTAL FEES ENCLOSED =				$170.00	
				Amount to be refunded	$
				Charged	$

a. X A check in the amount of $280 to cover the above fees and the one month Extension of Time is enclosed.
b. _ Please charge my Deposit Account No. 14-1060 in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.
c. X The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-1060.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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Washington, D.C. 20005-5701
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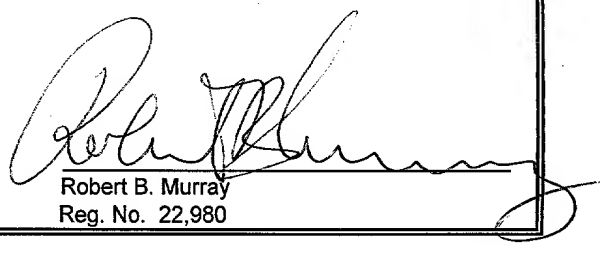


Robert B. Murray
Reg. No. 22,980

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

LUKAS-LASKEY, et al.

Serial Number: New Appln.

Filed: August 4, 1997

For: USE OF CARBAZOLE COMPOUNDS FOR THE TREATMENT OF CONGESTIVE HEART FAILURE

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

August 4, 1997

Sir:

Prior to initial examination, please amend the above-identified application as follows:

IN THE CLAIMS:

Please cancel claims 1-14 without prejudice or disclaimer.

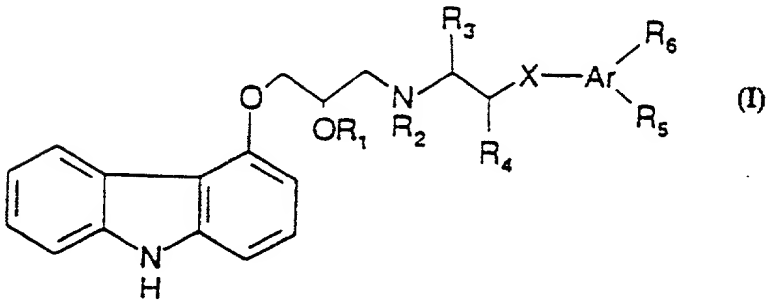
Please add new claims 15 - 41 as follows:

--15. A method of treating to decrease mortality resulting from congestive heart failure in a patient in need of such treatment, said method comprising administering to said patient a congestive heart failure mortality decreasing effective amount of a compound which is both a β-adrenoreceptor antagonist and a α_1-adrenoreceptor antagonist alone or in combination with at least one other therapeutic agent.

16. A method as recited in claim 15, wherein said patient is a mammal.

17. A method as recited in claim 15, further comprising administering to said patient at least one other therapeutic agent selected from the group consisting of angiotensin converting enzyme inhibitors, diuretics and cardiac glycosides.

18. A method as recited in claim 15, wherein said compound is a compound of formula I:



(I)

wherein:

R_1 is hydrogen, lower alkanoyl of from 1 to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of from 1 to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of from 1 to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of from 1 to 6 carbon atoms, or, where X is oxygen, R_4 together with R_5 can also be $-CH_2-O-$

X is a valency bond, $-CH_2-$, oxygen or sulfur;

Ar is phenyl, naphthyl, indanyl or tetrahydronaphthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine hydroxyl, lower alkyl of from 1 to 6 carbon atoms, a $-CONH_2$ group, lower alkoxy of from 1 to 6 carbon atoms, benzyloxy, lower alkylthio of from 1 to 6 carbon atoms and lower alkylsulphonyl of from 1 to 6 carbon atoms; or R_5 and R_6 together represent methylenedioxy;

or a pharmaceutically acceptable salt thereof.

19. A method as recited in claim 18, further comprising administering to said patient at least one other therapeutic agent selected from the group consisting of angiotensin converting enzyme inhibitors, diuretics and cardiac glycosides.

20. A method as recited in claim 15, wherein said compound is carvedilol.

21. A method as recited in claim 17, wherein said compound is carvedilol.

22. A method as recited in claim 15, wherein said step of administering comprises administering to said patient unit dosages once or twice daily, for a period of from 7 to 28 days, said unit dosages each comprising a pharmaceutical formulation comprising carvedilol in an amount of

about 3.125 mg or about 6.25 mg.

23. A method as recited in claim 15, wherein said step of administering comprises administering to said patient unit dosages once or twice daily, for a period of from 7 to 28 days, said unit dosages each comprising a pharmaceutical formulation comprising about 12.5 mg of carvedilol.

24. A method as recited in claim 15, wherein said step of administering comprises administering to said patient unit dosages once or twice daily, each said unit dosage comprising a pharmaceutical formulation comprising carvedilol in an amount of about 25.0 mg or about 50.0 mg.

25. A method as recited in claim 15, wherein said step of administering comprises administering to said patient daily dosages of said compound in an amount of from about 1.0 mg to about 30.0 mg.

26. A method as recited in claim 15, wherein said step of administering comprises administering to said patient daily dosages of said compound in an amount of from about 2.0 mg to about 70.0 mg.

27. A method as recited in claim 15, wherein said step of administering comprises administering to said patient daily dosages of said compound in an amount of from about 10.0 mg to about 100.0 mg.

28. A method as recited in claim 17, wherein said angiotensin converting enzyme inhibitor is selected from the group consisting of captopril, lisinopril, fosinopril, enalapril and pharmaceutically acceptable salts of captopril, lisinopril, fosinopril and enalapril.

29. A method as recited in claim 17, wherein said diuretic is selected from the group consisting of hydrochlorothiazide, torasemide, furosemide, and pharmaceutically acceptable salts of hydrochlorothiazide, torasemide and furosemide.

30. A method as recited in claim 17, wherein said cardiac glycoside is selected from the group consisting of digoxin, β-methyl-digoxin and digitoxin.

31. A method of treating congestive heart failure in a patient in need of such treatment, said method comprising administering to said patient first dosages once or twice daily, for a period of from 7 to 28 days, said first dosages each comprising a pharmaceutical formulation comprising carvedilol in an amount of about 3.125 mg or about 6.25 mg,

then administering to said patient second dosages once or twice daily, for a period of from 7 to 28 days, said second dosages each comprising a pharmaceutical formulation comprising carvedilol in an amount of about 12.5 mg, and

then administering to said patient third dosages once or twice daily, for a period of at least one day, said third dosages each comprising a pharmaceutical formulation comprising carvedilol in an amount of about 25.0 mg or about 50.0 mg.

32. A method as recited in claim 31, wherein at least one of said first, second and third dosages further comprise at least one other therapeutic agent selected from the group consisting of angiotensin converting enzyme inhibitors, diuretics and cardiac glycosides.

33. A method of treating congestive heart failure in a patient in need of such treatment, said method comprising:

administering to said patient first dosages daily for a period of from 7 to 28 days, said first dosages each comprising at least one pharmaceutical formulation comprising a compound which is both a β-adrenoreceptor antagonist and a α_1-adrenoreceptor antagonist,

then administering to said patient second dosages daily for a period of from 7 to 28 days, said second dosages each comprising at least one pharmaceutical formulation comprising a compound which is both a β-adrenoreceptor antagonist and a α_1-adrenoreceptor antagonist, once a day for a period of from 7 to 28 days, and

then administering to said patient third dosages daily for a period of at least one day, said third dosages each comprising at least one pharmaceutical formulation comprising a compound which is both a β-adrenoreceptor antagonist and a α_1-adrenoreceptor antagonist, said third dosages each comprising a daily maintenance dose in the range of from about 10 mg to about 100 mg of the compound,

said first dosages each comprising the compound which is both a β-adrenoreceptor antagonist and a α_1-adrenoreceptor antagonist in an amount which is 10-30% of said daily maintenance dose,

said second dosages each comprising the compound which is both a β-adrenoreceptor antagonist and a α_1-adrenoreceptor antagonist in an amount which is 20-70% of said daily

maintenance dose.

34. A unit dosage oral pharmaceutical formulation comprising 1.0 - 10.0 mg carvedilol.

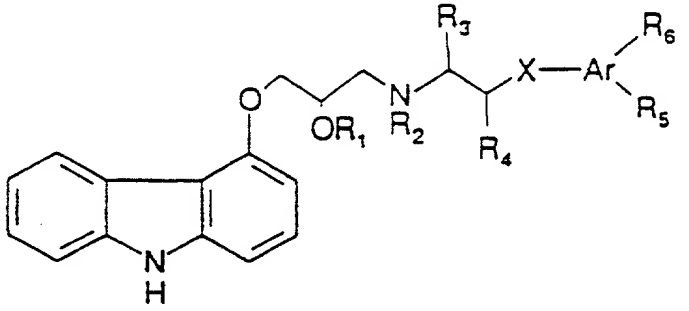
35. A unit dosage oral pharmaceutical formulation as recited in claim 34, wherein said formulation comprises 2.5 - 7.5 mg carvedilol.

36. A pharmaceutical formulation comprising:

a congestive heart failure treating effective amount of a compound which is both a β-adrenoreceptor antagonist and a α_1-adrenoreceptor antagonist for decreasing mortality; and

at least one other therapeutic agent selected from the group consisting of angiotensin converting enzyme inhibitors, diuretics and cardiac glycosides.

37. A pharmaceutical formulation as recited in claim 36, wherein said compound is a compound according to formula I:



(I)

wherein:

R_1 is hydrogen, lower alkanoyl of from 1 to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of from 1 to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of from 1 to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of from 1 to 6 carbon atoms, or, where X is oxygen, R_4 together with R_5 can also be $-CH_2-O-$

X is a valency bond, $-CH_2-$, oxygen or sulfur;

Ar is phenyl, naphthyl, indanyl or tetrahydronaphthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine hydroxyl, lower alkyl of from 1 to 6 carbon atoms, a $-CONH_2$ group, lower alkoxy of from 1 to 6 carbon atoms, benzyloxy, lower alkylthio of from 1 to 6 carbon atoms and lower alkylsulphonyl of from 1 to 6 carbon atoms; or R_5 and R_6 together represent methylenedioxy;

or a pharmaceutically acceptable salt thereof.

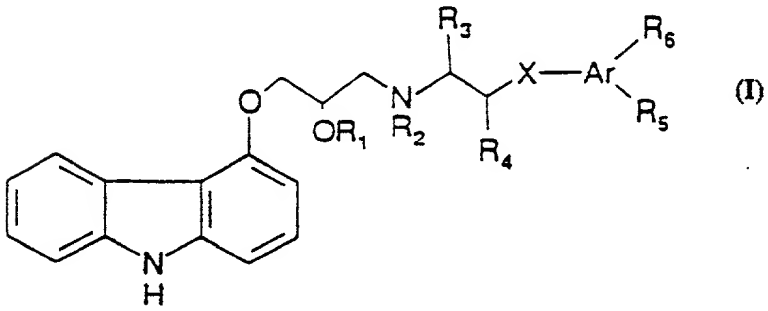
38. A pharmaceutical formulation as recited in claim 36, wherein said compound is carvedilol.

39. A kit comprising:

unit dosages of a congestive heart failure treating effective amount of a compound which is both a β-adrenoreceptor antagonist and a α_1-adrenoreceptor antagonist for decreasing mortality; and

unit dosages of at least one other therapeutic agent selected from the group consisting of angiotensin converting enzyme inhibitors, diuretics and cardiac glycosides.

40. A kit as recited in claim 39, wherein said compound is a compound according to formula I:



(I)

wherein:

R_1 is hydrogen, lower alkanoyl of from 1 to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of from 1 to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of from 1 to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of from 1 to 6 carbon atoms, or, where X is oxygen, R_4

together with R_5 can also be $-CH_2-O-$

X is a valency bond, $-CH_2-$, oxygen or sulfur;

Ar is phenyl, naphthyl, indanyl or tetrahydronaphthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine hydroxyl, lower alkyl of from 1 to 6 carbon atoms, a $-CONH_2$ group, lower alkoxy of from 1 to 6 carbon atoms, benzyloxy, lower alkylthio of from 1 to 6 carbon atoms and lower alkylsulphonyl of from 1 to 6 carbon atoms; or R_5 and R_6 together represent methylenedioxy;

or a pharmaceutically acceptable salt thereof.

41. A kit as recited in claim 39, wherein said compound is carvedilol.--

REMARKS

Claims 15 - 41 are added and original claims 1 - 14 are canceled in order to present claims which more particularly define the claimed subject matter, and to present claims which conform with formal U.S. requirements.

Favorable consideration of claims 15 - 41 is solicited.

Should it be deemed that any further action by the applicants could place this application in better condition for allowance, the Examiner is invited to telephone the undersigned at the number listed below.

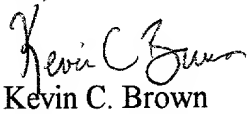
In the event this paper is not timely filed, applicants hereby petition for an appropriate

extension of time. The fee for this extension may be charged to our Deposit Account No. 14-1060, along with any other additional fees which may be required with respect to this paper.

Should any additional fees be due with respect to this paper, such fees may be charged to Counsel's Deposit Account No. 14-1060.

Respectfully submitted,

NIKAIDO, MARMELSTEIN, MURRAY & ORAM LLP



Kevin C. Brown
Attorney for Applicant
Registration No. 32,402

Atty. Docket No. P1614-7038
Metropolitan Square
655 Fifteenth Street, N.W.
Suite 330 - G-Street Lobby
Washington, D.C. 20005-5701
(202) 638-5000
KCB/drd

USE OF CARBAZOLE COMPOUNDS FOR THE TREATMENT OF CONGESTIVE HEART FAILURE

Field of the Invention

The present invention relates to a new method of treatment using compounds which are dual non-selective ß-adrenoceptor and α_1-adrenoceptor antagonists, in particular the carbazolyl-(4)-oxypropanolamine compounds of Formula I, preferably carvedilol, for decreasing the mortality of patients suffering from congestive heart failure (CHF). The invention also relates to a method of treatment using compounds which are dual non-selective ß-adrenoceptor and α_1-adrenoceptor antagonists, in particular the carbazolyl-(4)-oxypropanolamine compounds of Formula I, preferably carvedilol, in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of angiotensin converting enzyme (ACE) inhibitors, diuretics, and cardiac glycosides, for decreasing the mortality of patients suffering from CHF. The invention further relates to an incremental application scheme for administering compounds which are β-adrenoreceptor and α_1-adrenoreceptor antagonists.

Background of the Invention

Congestive heart failure occurs as a result of impaired pumping capability of the heart and is associated with abnormal retention of water and sodium. Traditionally, treatment of chronic mild failure has included limitation of physical activity, restriction of salt intake, and the use of a diuretic. If these measures are not suffcient, a cardiac glycoside, which is an agent that increases the force of mycardial contraction, is typically added to the treatment regimen.

Subsequently, angiotensin converting enzyme inhibitors, which are compounds that prevent the conversion of angiotensin I into the pressor-active angiotensin II, are prescribed for chronic treatment of congestive heart failure, in conjunction with a diuretic, a cardiac glycoside, or both.

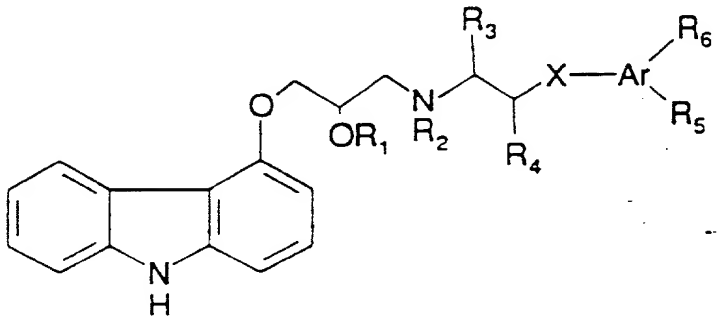
Also, congestive heart failure is a well-known cardiac disorder which results in an excess mortality. Applefeld, M.M., (1986) Am. J. Med., 80, Suppl. 2B, 73-77. Therefore, therapeutic agents that would decrease the mortality resulting from CHF in patients suffering therefrom are highly desirable.

Summary of the Invention

The present invention provides a new use of compounds which are dual non-selective ß-adrenoceptor and α_1-adrenoceptor antagonists for the preparation of medicaments for the treatment of congestive heart failure. In particular, the carbazolyl-(4)-oxypropanolamine compounds of Formula I are preferred, alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of ACE inhibitors, diuretics, and cardiac glycosides, as therapeutics for decreasing mortality resulting from congestive heart failure in mammals, particular. In particular, the present invention preferably provides a method of treatment, alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of ACE inhibitors, diuretics, and cardiac glycosides, for the compound of Formula I wherein R_1 is -H, R_2 is -H, R_3 is -H, R_4 is -H, X is 0, Ar is phenyl, R_5 is ortho -$0CH_3$, and R_6 is -H, said compound being better known as carvedilol, which is (1-(carbazol-4-yloxy-3-[[2-(2-methoxyphenoxy) ethyl]amino]2-propanol), or a pharmaceutically acceptable salt thereof.

Detailed Description of the Invention

U.S. Pat. No. 4,503,067 discloses carbazolyl-(4)-oxypropanolamine compounds of Formula I:



(I)

wherein

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent $-CH_2-O-$;

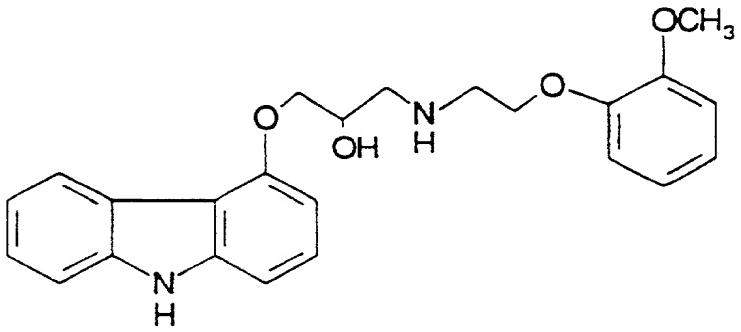
X is a valency bond, $-CH_2$, oxygen or sulfur;

Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a $-CONH_2-$ group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphonyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R_5 and R_6 together represent methylenedioxy; and pharmaceutically acceptable salts thereof.

This patent further discloses a compound of Formula I, better known as carvedilol, which is (1-(carbazol-4-yloxy-3-[[2-(2-methoxyphenoxy)ethyl]amino](2-propanol), having the structure shown in Formula II:



(II)

Formula I compounds, of which carvedilol is exemplary, are novel multiple action drugs useful in the treatment of mild to moderate hypertension. Carvedilol is known to be both a competitive non-selective ß-adrenoceptor antagonist and a vasodilator, and is also a calcium channel antagonist at higher concentrations. The vasodilatory actions of carvedilol result primarily from α_1-adrenoceptor blockade, whereas the ß-adrenoceptor blocking activity of the drug prevents reflex tachycardia when used in the treatment of hypertension. These multiple actions of carvedilol are responsible for the antihypertensive efficacy of the drug in animals, particularly in humans. See Willette, R.N., Sauermelch, C.F. & Ruffolo, R.R., Jr. (1990) Eur. J. Pharmacol., 176, 237-240; Nichols, A.J., Gellai, M. & Ruffolo, R.R., Jr. (1991) Fundam. Clin. Pharmacol., 5, 25-38; Ruffolo,

R.R., Jr., Gellai, M., Hieble, J.P., Willette, R.N. & Nichols, A.J. (1990) Eur. J. Clin. Pharmacol., 38, S82-588; Ruffolo, R.R., Jr., Boyle, D.A., Venuti, R.P. & Lukas, M.A. (1991) Drugs of Today, 27, 465-492; and Yue, T.-L., Cheng, H., Lysko, P.G., Mckenna, P.J., Feuerstein, R., Gu, J., Lysko, K.A., Davis, L.L. & Feuerstein, G. (1992) J. Pharmacol. Exp. Ther., 263, 92-98.

The antihypertensive action of carvedilol is mediated primarily by decreasing total peripheral vascular resistance without causing the concomitant reflex changes in heart rate commonly associated with other antihypertensive agents. Willette, R.N., et al. supra; Nichols, A.J., et al. supra; Ruffolo, R.R., Jr., Gellai, M., Hieble, J.P., Willette, R.N. & Nichols, A.J. (1990) Eur. J. Clin. Pharmacol., 38, S82-S88. Carvedilol also markedly reduces infarct size in rat, canine and porcine models of acute myocardial infarction, Ruffolo, R.R., Jr., et al., Drugs of Today, supra, possibly as a consequence of its antioxidant action in attenuating oxygen free radical-initiated lipid peroxidation. Yue, T.-L., et al. supra.

Recently, it has been discovered in clinical studies that pharmaceutical compounds which are dual non-selective ß-adrenoceptor and α_1-adrenoceptor antagonists, in particular the compounds of Formula I, preferably carvedilol, alone or in conjunction with conventional agents, said agents being ACE inhibitors, diuretics, and cardiac glycosides, are effective therapeutic agents for treating CHF. The use of agents, such as carvedilol in treating CHF is surprising, since, in general, ß-blockers are contraindicated in patients suffering from heart failure, because ß-blockers are known to have undesirable cardiodepressive effects. The most surprising observation from the studies in which the instant compounds were used to treat CHF is that said compounds, in particular carvedilol, are able to decrease the mortality resulting from CHF in humans by about 67 percent. Furthermore, this result is present across all classifications of CHF and both etiologies (eschemic and non-eschemic). This result is surprising since two recent mortality studies using the ß-blockers metoprolol (Waagstein, et al., (1993) Lancet, 342, 1441-1446) and bisoprolol (CIBIS investigators and committees, (1994) Circulation, 90, 1765-1773) in the

treatment of CHF showed no difference in mortality between drug-treated patients and placebo-treated patients.

According to the method of treatment of the present invention, the desirable therapeutic effect of the compounds of Formula I, particularly carvedilol, may be augmented by using any one of said compounds; or any pharmaceutically acceptable salt of said compounds, in conjunction with ACE inhibitors, diuretics, and cardiac glycosides, which are effective therapeutic agents for the treatment of CHF. In particular, the preferred ACE inhibitors of the present invention are selected from the group consisting of captopril, lisinopril, fosinopril and enalapril, or any pharmaceutically acceptable salts thereof and the preferred diuretics of the present invention are hydrochlorothiazide furosemide, or torasemide or any pharmaceutically acceptable salts thereof. The preferred cardiac glycosides of the present invention are digoxin, β-methyldigoxin or digitoxin. The desireable therapeutic benefits of the compounds of Formula I, particularly carvedilol, are additive with those of such ACE inhibitors, or diuretics, or cardiac glycosides when administered in combination therewith. Captopril is commercially available from E.R. Squibb & Sons, Inc. Lisinopril, enalapril and hydrochlorothiazide are commercially available from Merck & Co. Furosemide is commercially available from Hoechst-Roussel Pharmaceuticals, Inc. Digoxin is commercially available from Burroughs Wellcome Co. and Boehringer Mannheim GmbH. Digitoxin, β-Methyldigoxin, fosinopril and torasemide are commercially available from Boehringer Mannheim GmbH.

Compounds of Formula I may be conveniently prepared as described in U.S. Pat. No. 4,503,067. Carvedilol is commercially available from SmithKline Beecham Corporation and Boehringer Mannheim GmbH (Germany).

Pharmaceutical compositions of the compounds of Formula I, including carvedilol, alone or in combination with ACE inhibitors, or diuretics, or cardiac glycosides may be administered to patients according to the present invention in any medically acceptable manner, preferably orally. For parenteral administration, the pharmaceutical composition will be in the form of a sterile injectable liquid stored in a suitable container such as an

ampoule, or in the form of an aqueous or nonaqueous liquid suspension. The nature and composition of the pharmaceutical carrier, diluent or excipient will, of course, depend on the intended route of administration, for example whether by intravenous or intramuscular injection.

Pharmaceutical compositions of the compounds of Formula I for use according to the present invention may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation is generally a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as ethanol, polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternatively, these compounds may be encapsulated, tableted or prepared in a emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, peanut oil, olive oil, glycerin, saline, ethanol, and water. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension.

Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

Compounds having the above-mentioned dual properties are preferably administered following a three-stage application scheme. This scheme is characterized by the fact that incremental dosages of the active ingredient are administered to patients over a certain period of time, until the regular maintenance dosage is received. If this maintenance dosage is defined as the setting value being 100 %, it was found that the application regimen in a first phase should extend for a period of 7 - 28 days, whereby only 10-30 % of the setting dose are administered. Following this phase, a second application regimen should follow, wherein a dosage of 20 - 70 % of the setting dose is administered to the patient for a period of 7 - 28 days. After termination of this phase, the third application period follows, wherein the daily complete setting dose (maintenance dose) is administered. The daily maintenance dose can vary between 10 - 100 mg of said active ingredient.

In case of carvedilol, dosing in humans for the treatment of disease according to the present invention should not exceed a dosage range of from about 3.125 to about 50 mg of the compounds of Formula I, particularly carvedilol, preferably given twice daily. As one of ordinary skill in the art will readily comprehend, the patient should be started on a low dosage regimen of the desired compound of Formula I, particularly carvedilol, and monitered for well-known symptoms of intolerance, e.g., fainting, to such compound. Once the patient is found to tolerate such compound, the patient should be brought slowly and incrementally up to the maintenance dose. The preferred course of treatment is to start the patient on a dosage regimen with formulations which contain either 3.125 or 6.25 mg of active compound per single unit, preferably given twice daily, for 7 - 28 days. The choice of initial dosage most appropriate for the particular patient is determined by the practitioner using well-known medical principles, including, but not limited to, body weight. In the event that the patient exhibits medically acceptable tolerance of the compound for two weeks, the dosage is doubled at the end of the two weeks and the patient is maintained at the new, higher dosage for an additional period,

preferably to two more weeks. and observed for signs of intolerance. This course is continued until the patient is brought to a maintenance dose. The preferred maintenance dose is 25.0 mg of active compound per single unit. preferably given twice daily. for patients having a body weight of up to 85 kg. For patients having a body weight of over 85 kg. the maintenance dose is between about 25.0 mg and about 50.0 mg, preferably given twice daily; preferably about 50 0 mg of active compound per single unit. preferably given twice daily.

The present invention relates also to method of treatment for decreasing mortality resulting from congestive heart failure in mammals comprising internally administering to said mammal in need thereof an effective amount of carvedilol according to the following schedule:

(a) a pharmaceutical formulation which contains either 3.125 or 6.25 mg carvedilol per single unit for a period of 7 - 28 days, given once or twice daily.

(b) thereafter a pharmaceutical formulation which contains 12.5 mg carvedilol per single unit for a period of additional 7 - 28 days, given once or twice daily. and

(c) finally a pharmaceutical formulation which contains either 25.0 or 50.0 mg carvedilol per single unit, given once or twice daily as a maintenance dose.

Dosing in humans for the treatment of disease according to the present invention includes the combination of compounds of Formula I with conventional agents. For example. the usual adult dosage of hydrochlorothiazide is 25 - 100 mg daily as a single dose or divided dose. The recommended starting dose for enalapril is 2.5 mg administered once or twice daily. The usual therapeutic dosing range for enalapril is 5 - 20 mg daily, given as a single dose or two divided doses. For most patients the usual initial daily dosage of captopril is 25 mg three times per day (tid), with most patients having a satisfactory clinical improvement at 50 or 100 mg three times per day (tid).

It will be appreciated that the actual preferred dosages of the compounds being used in the compositions of this invention will vary according to the particular composition formulated, the mode of administration, the particular site of administration and the host being treated.

No unacceptable toxicological effects are expected when the compounds of Formula I, including the compound of Formula II, are used according to the present invention. The example which follows is intended in no way to limit the scope of this invention, but is provided to illustrate how to use the compounds of this invention. Many other embodiments will be readily apparent to those skilled in the art.

Experimental

Mortality Studies in CHF Patients

Summary. To determine if ß-adrenergic blockade might inhibit the deleterious effects of the sympathetic nervous system on survival in heart failure (CHF), 1052 patients with CHF were prospectively enrolled into a multicenter trial program, in which patients were randomly assigned (double-blind) to 6-12 months' treatment with placebo (PBO) or carvedilol (CRV),. After a common screening period, patients with class II-IV CHF (see next paragraph for the definitions of the classification of CI) and an ejection fraction < 0.35 were assigned to one of four protocols based on performance on a 6-minute walk test. PBO or CRV was added to existing therapy with digoxin, diuretics and an ACE inhibitor. All-cause mortality was monitored by a prospectively constituted Data and Safety Monitoring Board (DSMB). After 25 months of enrollment, the DSMB recommended termination of the program because of a favorable effect of CRV on survival. By intention-to-eat, mortality was 8.2% in the PBO group but only 2.9% in the CRV group (P = 0.0001, Cochran-Mantel-Haensel analysis). This represented a reduction in risk of death by CRV of 67% (95% CI: 42% to 81 %). The treatment effect

was similar in patients with class II and class III-IV symptoms. Mortality was -educed in class II patients from 5.9% to 1.9%, a 68% reduction (95% CI: 20% to 97%) [P = 0.015,), and in class III-IV patients from 11.0% to 4.2%, a 67% reduction (95% CI: 30% to 84%), [P = 0.004, log-rank]. Importantly, the effect of CRV was similar in ischemic heart disease (risk reduced by 67%, P = 0.003) and in nonischemic dilated cardiomyopathy (risk reduced by 67%, P = 0.014). In conclusion, the addition of CRV to conventional therapy is associated with a substantial (67%) reduction in the mortality of patients with chronic CHF. The treatment effect is seen across a broad range of severity and etiology of disease.

As used herein, by "Class II CHF" is meant patients with cardiac disease resulting in slight or moderate limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain. By "Class III CHF" is meant patients with cardiac disease resulting in marked limitations of physical activity They are comfortable at rest. Less than ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain. By "Class IV CI" is meant patients with cardiac disease resulting in inability to car on any physical activity without discomfort, symptoms or cardiac insufficiency, or of the anginal syndrome. By "less than ordinary physical activity" is meant climbing one flight of stairs, or walking two hundred yards.

Design of Study. Patients on background therapy with diuretics, ACE inhibitors and/or digoxin were stratified on the basis of baseline submaximal exercise performance, into one of four trials:

- study 220, a dose response study in moderate (NYHA II-IV) CHF with exercise testing as a primary endpoint

- study 221, a dose titration study in moderate (NYHA II-IV) CI with exercise testing as a primary endpoint

- study 239, a dose titration study in severe (NYHA III-IV) CHF with quality of life as a primary endpoint

- study 240, a dose titration study in mild (NYHA II-III) CHF with progression of CHF as a primary endpoint

Sixty-four centers in the US participated in the trial program. All sites conducted protocols 239 and 240, while 33 performed protocol 220 and 31 performed protocol 221.

Although each trial had its own individual objectives, the overall program objective defined prospectively was evaluation of all-cause mortality. Based upon a projected enrollment of 1100 patients, the program had 90% power to detect a 50% reduction in mortality (two-sided) between carvedilol and placebo, assuming a mortality rate in the placebo group of 12% over the duration of the trials $\alpha = 0.05$).

Randomization was preceded by a screening and challenge period common to the four protocols The purpose of the screening period was to qualify patients for study entry, obtain reproducible baseline measurements, and stratify patients into the appropriate trial based on submaximal exercise testing. During the challenge period, patients received low-dose open-label carvedilol (6.25 mg b.i.d.) for two weeks. Patients unable to tolerate this dose did not proceed to randomization. Patients tolerating low-dose carvedilol were then randomized to blinded medication (carvedilol or placebo) with the dose titrated over several weeks in the range of 6.25 to 50 mg b.i.d. (or equivalent level of placebo). The maintenance phase of each study ranged from six to 12 months, after which patients had the option of receiving open-label carvedilol in an extension study.

Results. The analysis presented below corresponds to the data set on which the DSMB made the recommendation to terminate the trials. Included in this intent-to-eat analysis are all patients enrolled in the US trials as of January 20, 1995; 624 receiving carvedilol

and 356 placebo. An analysis of baseline patient characteristics (Table 1) shows good balance between the randomized groups.

Table 1: US Carvedilol Heart Failure Trials - Baseline Characteristics

Characteristic	Placebo (n = 356)	Carvedilol (n = 624)
Age, mean + SD (years)	59.9+11.7	58.8+11.8
Sex (% men)	62%	62%
Etiology (% ischemic)	43%	40%
Severity of CHF		
Class II	41%	41%
Class III-IV	40%	39%
Unknown	19%	20%
LV ejection fraction, mean + SD	0.22 + 0.07	0.23 + 0.08
6 Minute walk (m + SD)	373+88	379+81
Blood pressure (mmHg)	115/73	115/73
Heart rate (bpm + SD)	85 ± 13	86 ± 13

The overall mortality results for the program are shown in Table 2. All deaths that occurred during the intent-to-treat period are included. Treatment with carvedilol resulted in a 67% reduction in the risk of all-cause morality. Analysis of mortality by certain baseline characteristics shows this to be a broad effect regardless of severity or etiology of CI. The effect was uniform in patients with mild heart failure or moderate to severe heart failure. Similarly, the mortality reduction was equivalent in patients with ischemic or non-ischemic heart failure.

Table 2: Evaluation of Mortality in US Carvedilol CHF Studies

	Carvedilol	Placebo	Risk reduction (95 % CI)	p value*
All Cause Mortality	18/624 (2.9 %)	29/356 (8.2 %)	67 % (42 - 81)	< 0.001
Class II CHF	7/361 (1.9 %)	12/202 (5.9 %)	68 % (20 - 97)	0.015
Class III-IV CHF	11/263 (4.2 %)	17/154 (11.0 %)	66 % (30 - 84)	0.004
Ischemic Etiology	10/311 (3.2 %)	16/178 (8.9 %)	67 % (32 -85)	0.003
Non-Ischemic Etiology	8/313 (2.5 %)	13/178 (7.3 %)	67 % (20 - 86)	0.014

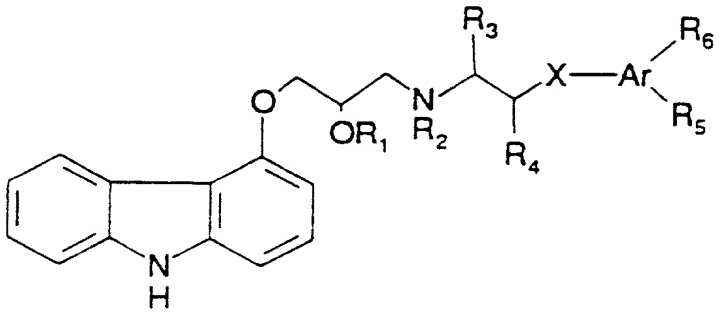
*Cochran-Mantel-Haensel Anatysis

The foregoing is illustrative of the use of the compounds of this invention. This invention, however, is not limited to the precise embodiment described herein, but encompasses all modifications within the scope of the claims which follow.

Claims

1. The use of a compound which is both a β-adrenoreceptor antagonist and a α_1-adrenoreceptor antagonists for the manufacture of a medicament for decreasing mortality resulting from congestive heart failure in mammals, alone or in conjunction with one or more other therapeutic agents, said agents selected from the group consisting of an angiotensin converting enzyme inhibitor, a diuretic and a cardiac glycosides

2. The use of a compound according to claim 1, wherein said compound is subject of formula I



(I)

wherein

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms. or when X is oxygen. R_4 together with R_5 can represent $-CH_2-O-$.

X is a valency bond, $-CH_2$, oxygen or sulfur;

Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a $-CONH_2-$ group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphonyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R_5 and R_6 together represent methylenedioxy; and pharmaceutically acceptable salts thereof.

3 The use of a compound according to claim 1 or 2, wherein said compound is carvedilol

4. The use of a compound according to claim 3, whereby a pharmaceutical formulation containing either 3.125 or 6.25 mg carvedilol in a single unit are administered for a period of 7 - 28 days, once or twice daily as an initial dose.

5. The use of a compound according to claim 3, whereby a pharmaceutical formulation containing 12.5 mg carvedilol in a single unit are administered for a period of 7 - 28 days, once or twice daily.

6. The use of a compound according to claim 3, whereby a pharmaceutical formulation containing either 25.0 or 50.0 mg carvedilol in a single unit are administered once or twice as a maintenance dose.

7 The use of a compound according to claim 1, wherein said ACE inhibitor is selected from the group consisting of captopril, lisinopril, fosinopril or enalapril, or any pharmaceutically acceptable salt thereof.

8 The use of a compound according to claim 1, wherein said diuretic is selected from the group consisting of hydrochlorothiazide, torasemide or furosemide, or any pharmaceutically acceptable salt thereof.

9 The use of a compound according to claim 1, wherein said cardiac glycoside is selected from the group consisting of digoxin, β-methyl-digoxin or digitoxin.

10 The use of carvedilol for the manufacture of a medicament for decreasing mortality resulting from congestive heart failure in mammals according to the following regimen:

(a) administering a pharmaceutical formulation which contains either 3.125 or 6.25 mg carvedilol per single unit for a period of 7 - 28 days, given once or twice daily,

(b) administering thereafter a pharmaceutical formulation which contains 12.5 mg carvedilol per single unit for a period of additional 7 - 28 days, given once or twice daily and

(c) administering finally a pharmaceutical formulation which contains either 25.0 or 50.0 mg carvedilol per single unit, given once or twice daily as a maintenance dose.

11. The use of carvedilol according to claim 10, whereby carvedilol is administered in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of an angiotensin converting enzyme inhibitor, a diuretic and a cardiac glycoside.

12. Use of a compound according to claim 1 for the preparation of a medicament for the treatment of CHF to be administered in a daily maintenance dose of 10 - 100 mg, said medicament being administered in incremental dosage schems comprising three dose regimens, the first regimen comprising administering an amount of 10 - 30 % of the daily maintenance dose of the compound for a period of 7 - 28 days, the second regimen comprising administering an amount of 20 - 70 % of said daily dose for a period of 7 - 28 days and a third regimen comprising administering 100 % of said daily dose starting after termination of the second regimen.

N, M, M & O Docket No. P1614-7038 NIKAIDO, MARMELSTEIN, MURRAY & ORAM LLP

Declaration For U.S. Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention **entitled** (Insert Title) USE OF CARBAZOLE COMPOUNDS FOR THE TREATMENT OF CONGESTIVE HEART FAILURE the specification of which is attached hereto unless the following box is checked:

☒ was filed on February 7, 1996 as United States Application Number or PCT International Application Number PCT/EP96/00498 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate or PCT International Application having a filing date before that of the application(s) for which priority is claimed:

(List prior foreign applications. See note A on back of this page)	(Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed
	195 03 995.5	DE	8/2/95	☒ Yes ☐ No
				☐ Yes ☐ No
				☐ Yes ☐ No

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

(Application Number)	(Filing Date)

(See Note B on back of this page) ☐ See attached list for additional prior foreign or provisional applications.

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) or §365(c) of any PCT International application(s) designating the United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) (U.S. or PCT) in the manner provided by the first paragraph of 35, U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(List prior U.S. Applications or PCT International applications designating the U.S.)	(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
	08/483,635	7/6/95	

And I hereby appoint as principal attorneys David T. Nikaido, Reg. No. 22,663; Charles M. Marmelstein, Reg. No. 25,895; George E. Oram, Jr., Reg. No. 27,931; Robert B. Murray, Reg. No. 22,980; Martin S. Postman, Reg. No. 18,570; E. Marcie Emas, Reg. No. 32,131; Douglas H. Goldhush, Reg. No. 33,125; Kevin C. Brown, Reg. No. 32,402; Monica Chin Kitts, Reg. No. 36,105; Sharon N. Klesner, Reg. No. 36,335; and Richard J. Berman, Reg. No. 39,107.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

(See Note C on back of this page)

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